80. (Twice amended) [A] An artificial lipid membrane comprising [isolated or] purified or isolated ICAM-1 [substantially free of natural protein contaminants], wherein said [isolated or] purified or isolated ICAM-1 is derived from human cells or tissues, is substantially free of natural protein contaminants in said artificial lipid membrane, and is capable of binding to LFA-1, Mac-1, or p150,95.

81. (Thrice amended) [A] An artificial lipid membrane as claimed in claim 80, wherein said purified or isolated ICAM-1 [specifically] binds to LFA-1.

## *Remarks*

Reexamination and reconsideration of this application are respectfully requested. In this amendment Applicants have cancelled claims 79, 83, and 87-98 without disclaimer or prejudice. Applicants also acknowledge the Examiner's entry of the amendment filed July 6, 1998, pursuant to 37 C.F.R. § 1.129(a). Therefore, following the entry of this amendment, claims 71-73, 75-78, and 80-82 will be pending and subject to examination.

In the Office Action, the Examiner rejected claim 79 under 35 U.S.C. § 112, fourth paragraph, alleging that this claim fails to further limit the claimed subject matter of independent claim 71. In support of this rejection the Examiner states "[t]he ICAM-1 products of claim 1 [sic, 71] would inherently have the same amino acid sequence as that of Fig. 8 as claimed in claim 79. Therefore, claim 79 does not further limit the subject matter of claim 71." (Paper No. 14 at 2.) Applicants respectfully traverse this ground for rejection.

Applicants invention as presently claimed relates, *inter alia*, to a purified or isolated ICAM-1 preparation derived from a human source. While the amino acid sequence depicted in Figure 8 is a human ICAM-1 sequence, the Examiner has not presented any evidence to establish that all human ICAM-1's share the identical amino acid sequence. In fact, some minor variations in sequence, *e.g.*, caused by somatic mutations, may be expected. Nevertheless, in an effort to advance prosecution, Applicants have cancelled claim 79 rendering this rejection moot.

The Examiner also rejected claim 73 under 35 U.S.C. § 112, fourth paragraph, alleging that this claim fails to further limit the claimed subject matter of independent claim 72. The Examiner alleges "[t]he term 'specifically bind' does not further limit the term used in claim 72 'bind'." (Paper No. 14 at 2.) In making this rejection, the Examiner has noted a typographical error that appeared in the Amendment filed on October 15, 1997. Both claims 72 and 73 were newly added to this application in an amendment filed on January 7, 1997. In the Amendment of October 15, 1997, an amendment of claim 72, inserting the word "specifically," was incorrectly identified as an amendment of claim 73. It is clear from the context that an amendment of claim 72 was intended , since the entire text of claim 72 was written out in the instructions to amend. Therefore, Applicants thank the Examiner for noting this error, and request that the record be clarified to reflect that claim 72 and not claim 73 was amended on October 15, 1997. In light of this clarification, this rejection has been rendered moot.

The Examiner rejected claim 71, under 35 U.S.C. § 112, first paragraph, alleging that the specification "fail[s] to describe so as to enable ICAM-1 having amino acid sequences other than the sequence of Fig. 8." (Paper No. 14 at 3.) In support of this rejection, the Examiner states "[t]here is no description of allelic variants, or mammalian homologs of ICAM-1 sequences, and it would have been unpredictable whether such variants exist. Thus, one with skill in the art

would not have had a reasonable expectation of being able to make and use variants of ICAM-1 other than those having the sequence of Fig. 8." (*Id.*) The Examiner similarly rejected claims 72--78 and 80-83. (*Id.* at 3-4.) Applicants respectfully traverse these rejections.

Applicants invention as presently claimed relates, *inter alia*, to a purified or isolated ICAM-1 preparation, where the ICAM-1 is derived from human cells or tissues. Thus, Applicants' invention as now claimed does not relate to ICAM-1's from non-human mammals.

The specification of parent Application No. 07/045,963, filed May 4, 1987 [hereinafter "the '963 priority application"], describes human ICAM-1 in a variety of ways. On pages 16-18 of the '963 priority application, a method of obtaining anti-ICAM-1 monoclonal antibodies is described. The '963 priority application then describes the purification of various forms of ICAM-1 using monoclonal antibody affinity chromatography from various human cells and tissues. ('963 priority application at 18-19.) The '963 priority application also defines human ICAM-1 functionally, in terms of its ability to bind LFA-1 and mediate inflammation. The human ICAM-1's isolated from different human cells and tissues are characterized by molecular weight and degree of glycosylation. ('963 priority application at 19-20.) Moreover the '963 priority application defines the term "ICAM-1" in terms of reactivity to a monoclonal antibody: "[t]he antigen bound by monoclonal antibody RR1/1 is defined as the intercellular adhesion molecule-1 (ICAM-1)." ('963 priority application at 39.) In light of this detailed structural and functional characterization of human ICAM-1 found in the '963 priority application, Applicants have clearly enabled the full scope of their invention as presently claimed. Therefore, Applicants respectfully request the Examiner to withdraw these grounds for rejection.

The Examiner rejected claims 71-73 and 79 under 35 U.S.C. § 102(b) for allegedly being anticipated by Tomassini, thesis 8624033 (1986) [hereinafter "the Tomassini thesis"] or Tomassini

*et al.*, *J. Virol.* 58:290-295 (1986) [hereinafter "the Tomassini article"]. In support of this rejection, the Examiner states that the rejected claims "are directed to purified or isolated ICAM-1 preparations capable of binding to LFA-1, Mac-1 or p150,95. Page 58 of the cited document teach 400-fold immunoaffinity purified 90 kDa HRRP (ICAM-1). The cited document is silent as to whether the 90 kDa HRRP product (ICAM-1) binds to a member of the LFA-1 family, but would inherently have this property as it would comprise the same binding site residues as the ICAM-1 products encompassed by the instant claim language." (Paper No. 14 at 4.) Applicants respectfully traverse this ground for rejection.

Both the Tomassini thesis and the Tomassini article discuss the same purification method of HRRP, using detergent solubilization followed by BioRad Affi-Gel affinity chromatography with anti-HRRP monoclonal antibodies coupled to the gel matrix. In the Tomassini article, the authors indicate "[r]epeated attempts to use radiolabeled HRV in place of receptor antibody in the RIA gave inconclusive results owing to poor virus binding." (Tomassini article at 292, col. 2, lines 18-21.) Thus, the purified HRRP receptor preparation relied on by the Examiner is not able to bind HRV. It is known that the binding site for LFA-1 and HRV overlap. (Specification at 121.) Due to this overlap in binding sites, one of ordinary skill in the art would expect that any disruption in structure from the purification procedure that would reduce or eliminate HRV binding would also reduce or eliminate LFA-1 binding. Therefore, one of ordinary skill in the art would not expect that the HRRP preparation of Tomassini would exhibit the ability to the bind ligands as recited in the pending claims. The Tomassini HRRP preparation, consequently, cannot anticipate the presently pending claims. In light of these arguments, Applicants respectfully request the Examiner to withdraw this ground for rejection.

The Examiner also rejected claims 71-73 and 75-79 under 35 U.S.C. § 103(a) for allegedly being unpatentable over the Tomassini thesis and the Tomassini article. The Examiner notes that several "claims encompass forms of ICAM-1 produced in different human tissues or by different human cell lines." (Paper No. 14 at 4.) In support of this rejection, the Examiner then states that the Tomassini article "indicates that the HRV receptor is ubiquitous in the human body, and thus one of ordinary skill in the art at the time of invention would have had a reasonable expectation of isolating HRRP (ICAM-1) from any tissue in the human body using the methods taught by the cited references for the purpose of studying [or] modulating the attachment of HRV to human tissues." (Paper No. 14 at 5.) Applicants respectfully traverse this ground for rejection.

As discussed *supra* in response to the previous rejection, the Tomassini thesis and the Tomassini article do not teach the isolation of HRRP in active form as presently claimed. No other art has been cited by the Examiner to establish the purification of HRRP in an active form. Therefore, the Examiner has failed to establish a *prima facie* case of obviousness and Applicants respectfully request that this ground for rejection be withdrawn.

The Examiner also rejected claims 80 and 81 under 35 U.S.C. § 102(b) for allegedly being anticipated by the Tomassini thesis or the Tomassini article. In support of this ground for rejection, the Examiner notes that "[t]he claims are directed to lipid membranes comprising isolated or purified ICAM-1. The cited references teach HeLa cell membrane preparations that bind to anti-HRRP (ICAM-1) antibody." (Paper No. 14 at 5, citations omitted.) Applicants respectfully traverse this ground for rejection.

Applicants' invention as presently claimed in claims 80-81 relates to artificial lipid membranes containing ICAM-1 capable of binding LFA-1, Mac-1, or p150,95. As discussed *supra*, the HRRP described in the Tomassini thesis and the Tomassini article has lost functional

activity. In addition, the Tomassini thesis and Tomassini article relate to HeLa cell membrane preparations, while the presently claimed invention relates to artificial lipid membranes. Therefore, the Tomassini thesis and Tomassini article do not anticipate the invention as presently claimed. Applicants therefore respectfully request the Examiner to withdraw this ground for rejection.

The U.S. Patent and Trademark Office is hereby authorized to charge any fee deficiency, or credit any overpayment, to our Deposit Account No. 19-0036. In the event an extension of time is necessary to prevent the abandonment of this application not accounted for herein, such an extension is specifically requested and the requisite fee should also be charged to our Deposit Account.

Respectfully submitted,

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